REMARKS/ARGUMENTS

The foregoing amendments in the specification and claims are of formal nature, and do not add new matter.

Prior to the present amendment, Claims 28-47 were pending in this application. With this amendment, Claims 28-30, 36-37 and 41-43 have been canceled without prejudice, Claims 31-35, 38-39 and 44 have been amended to clarify what Applicants have always regarded as their invention and new Claims 48-54 have been added. Claims 31-35, 38-40 and 44-54 are pending after entry of the instant amendment. Applicants expressly reserve the right to pursue any canceled matter in subsequent continuation, divisional or continuation-in-part applications.

The amendments to the specification and claims are fully supported by the specification and claims as originally filed and do not constitute new matter. In addition, new Claims 48-54 are fully supported by the specification as originally filed. Support for new Claims 48-54 can be found at least on page 205, lines 17-21, on page 282, lines 12-19 and on page 308, line 38 to page 309, line 7 of the specification.

In addition, Applicants request the PTO to take note of the Revocation and Power of Attorney and Change of Address filed on February 28, 2003, and kindly direct all future correspondence to the address indicated, *i.e.*, to:

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Priority Determination

According to the Examiner, "the claimed nucleic acid (SEQ ID NO:305 that encodes the PRO1558 protein) having utility in gene amplification assays has earliest priority to February 18, 2000 as disclosed in PCT/US/04342."

Applicants rely on the gene amplification assay (Example 143) for support of patentable utility. This data was first disclosed in International Application Serial No. PCT/US00/03565 filed on February 11, 2000, starting on page 138 (Example 26), the priority of which is claimed

in the present application. Accordingly, the present application is entitled to at least the February 11, 2000 priority.

Claim Objections

Claims 28-33, 38-39, and 41 are objected to for reciting "the nucleic acid sequence shown in Figure 171 (SEQ ID NO:305)" and "the full-length coding sequence of the nucleic acid sequence shown in Figure 171 (SEQ ID NO:305)" allegedly because "there does not appear to be a patentable distinction between the two sequences since both sequences comprises SEQ ID NO:305."

Applicants respectfully disagree and traverse the rejection.

Step "e" of Claims 28-33 recite "the nucleic acid sequence shown in Figure 171 (SEQ ID NO:305)", hence the claim comprises the entire length of SEQ ID NO:171. On the other hand, step "f" recites "the full-length coding sequence of the nucleic acid sequence shown in Figure 171 (SEQ ID NO:305)". Therefore, step "f" comprises only the coding sequence of the SEQ ID NO:179 and not the entire sequence of the SEQ ID NO:179. It is well understood in the art that a coding sequence begins at a start codon, "ATG", and ends at a stop codon, such as "TAG". The start and stop codons are underlined and clearly marked in Figure 171 (SEQ ID NO:305). Therefore, Applicants respectfully submit that steps "e" and "f" are patentably distinct.

Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present objection.

Claim Rejections Under 35 U.S.C. §101

The Examiner asserts that Claim 46, "as written, does not sufficiently distinguish over cells as they exist naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed products and naturally occurring products."

Without acquiescing to the Examiner's position in the current rejections, and without prejudice to further prosecution of the subject-matter in one or more continuation or divisional applications, Applicants have amended Claim 46 (and, as a consequence, those claims dependent from the same) to recite an "isolated host cell." Thus, the claimed cells are distinguished over cells in nature. Hence, Applicants respectfully request reconsideration and withdrawal of the present rejection.

Claim Rejections – 35 U.S.C. §112, Second Paragraph

Claim 42 is rejected under 35 U.S.C. §112, second paragraph, allegedly because the term "stringent conditions" are not defined by the claim.

Without acquiescing to these rejections, Applicants submit that the cancellation of Claims 41-43 renders the rejection of these claims (and, as a consequence, those claims dependent from the same) moot. Accordingly, Applicants request that the rejection of Claim 42 under 35 U.S.C. §112, second paragraph, be withdrawn.

Claim Rejections – 35 U.S.C. §112, First Paragraph (Written Description)

Claims 28-33, 36-37 and 41-47 are rejected under 35 U.S.C. §112, first paragraph, for alleged lack of sufficient written description. The Examiner noted that in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

In particular, the Examiner notes that "[t]he claims are drawn to nucleic acids having at least 80%, 85%, 90%, 95% or 99% sequence identity" with SEQ ID NO:305, but "the claims do not require that the polypeptide (and or nucleic acid sequence) possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature." Therefore, the Examiner concludes that "the written description is not commensurate in scope with the claims which read on nucleic acid variants and or fragments of SEQ ID NO:305 and or fragments of SEQ ID NO:305 and or nucleic acids encoding variants and or fragments of SEQ ID NO:306 including those that only encode extracellular domains."

Applicants submit that the cancellation of Claims 28-30 and 36-37 and 41-43 renders the rejection of these claims moot.

Further, without acquiescing to the propriety of this rejection, Applicants have amended Claims 31-32 to recite "the nucleic acid encoding said polypeptide is amplified in lung or colon tumors." The Example 14 of the Written Description Guidelines issued by the U.S. Patent Office clearly states that the protein variants meets the requirements of 35 U.S.C. §112, first paragraph, as providing adequate written description for the claimed invention even if the specification contemplates but does not exemplify variants of the protein if (1) the procedures for making such variant proteins is routine in the art, (2) the specification provides an assay for detecting the functional activity of the protein and (3) the variant proteins possess the specified functional

activity and at least 95% sequence identity to the reference sequence. Applicants submit that the instant specification evidences the actual reduction to practice of a full-length PRO1558 polypeptide of SEQ ID NO:306, with or without its signal sequence and its encoding nucleic acid of SEQ ID NO: 305. In addition, the specification provides detailed description about the cloning of variants and describes the gene amplification assay for testing nucleic acids in a PCR based assay. Thus, Applicants submit that the genus of nucleic acids that code for the polypeptide of SEQ ID NO:306 or variants of nucleic acid of SEQ ID NO:305 with at least 95% sequence identity, which possess the functional property of being "amplified in lung or colon tumors" would meet the requirement of 35 U.S.C. §112, first paragraph, as providing adequate written description.

Further, Claim 33, parts (a) and (b) have been canceled.

Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

Claim Rejections – 35 U.S.C. §112, First Paragraph (Enablement)

Claims 28-47 are rejected under 35 U.S.C. §112, first paragraph, allegedly for "failing to comply with the enablement requirement" since "[t]he claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art which it pertains, or with which it is most nearly connected, to make and/or use the invention."

In particular, the Examiner notes that "the specification teaches that several primary lung tumors exhibited amplification of the PRO1558 gene." However, in assessing the value of these gene amplification data, the Examiner notes that: "the specification teaches that the negative control consisted of DNA isolated from the blood cells of ten normal healthy individuals. However, the specification is silent as to any correlation between DNA isolated from lung cancer and DNA isolated from the blood." Therefore, the Examiner asserts that "one needs to know, *e.g.*, that the claimed sequence is present only in cancer tissue to the exclusion of the corresponding normal tissue", and concludes that "one of ordinary skill in the art would not be able to use the invention in a predictable manner[, because] it would require undue experimentation to practice the invention as claimed."

Applicants respectfully disagree and traverse the rejection.

Applicants submit that the cancellation of Claim 28-30, 36-37 and 41-43 renders the rejection of these claims moot.

First of all, As discussed above, Applicants rely on the gene amplification data for patentable utility for the PRO1558 polypeptide. Applicants respectfully submit that SEQ ID NO:305 encoding PRO1558 was amplified in five *lung tumor* and *lung tumor cell lines* (HF-000840, HF-000842, HF-001294, HF-001296 and HF-001299) and one *colon* tumor (HF-000795).

Secondly, Applicants respectfully submit that since the specification clearly provides that the PRO1558 gene was clearly amplified in six of the lung tumors, tumor cell lines and colon tumor. Therefore, contrary to the Examiner's assertion that one of ordinary skill in the art would not able to use the invention in a predictable manner, one skilled in the art would know exactly how to make and use the claimed nucleic acids for the diagnosis of lung and colon cancers; for example, by using diagnostic methods based on hybridization to such amplified sequences. As the M.P.E.P. states, "The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation" *In re Certain Limited-charge cell Culture Microcarriers, 221 USPQ 1165, 1174* (Int'l Trade Comm'n 1983), *aff'. sub nom., Massachusetts Institute of Technology v A.B. Fortia,* 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985) M.P.E.P. 2164.01.

Further, the Examiner contends that the "applicants are attempting to compare the expression of PRO1558 in lung tumor specimens versus its expression in a non-related tissue .... [and that] a true negative control would more than likely comprise the analysis of the expression of PRO1558 in the corresponding normal tissue." While Applicants agree with the Examiner that comparing the expression of PRO1558 in lung tumor with the expression of PRO1558 in normal lung tissue would also be a true negative control, Applicants respectfully submit that the negative control as used in the gene amplification in the present application is also considered a true negative control.

Applicants submit that the gene amplification data were obtained by comparing DNA from a variety of primary tumors, including breast, lung, colon, rectum, kidney, testis, lymph node and parathyroid tumors, and various tumor cell lines with pooled DNA from healthy donors. (See PCT/US00/03565, the priority of which is claimed in the present application). In

addition, as the Examiner noted, the samples for negative control were obtained from blood cells of healthy individuals, as it is usual in similar gene amplification assays. It appears to the Applicants that the Examiner's concern is that the positive results of the present application is an artifact caused by the different genetic compositions between the solid tissue and blood. However, the fact that the gene was only amplified in six of the lung and colon tumors and lung cell lines, but not in the control sample or in the other tumors or tumor cell lines (*e.g.*, breast tumor) clearly indicates that this is not the case. Otherwise, the PRO1558 gene would be expected to be expressed in all solid tumor tissues.

Therefore, based on the instant disclosure, which clearly details the amplification of the PRO1558 gene in a number of lung and colon tumors, and the advanced knowledge in the art at the time of filing, one skilled in the art would know exactly how to make and use the claimed nucleic acids for the diagnosis of lung and colon cancers; for example, by using diagnostic methods based on hybridization to such amplified sequences. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

Claim Rejections - 35 U.S.C. §102

Claims 41-43 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by EST Sequence Database, Accession No. AA584408, September 26, 1997..

Applicants respectfully submit that the cancellation of Claims 41-43 renders the rejection of these claims moot.

However, in response to an anticipated rejection for new Claims 48-54 under 35 U.S.C. §102(b) in view of Accession No. AA584408, Applicants respectfully that Claim 48 (and, as a consequence, those claims dependent from the same) to recite "[a]n isolated nucleic acid molecule consisting of an at least 20 nucleotides fragment of the nucleic acid sequence of SEQ ID NO:305, or a complement thereof, that specifically hybridizes under stringent conditions to ...." Applicants respectfully submit that the art-recognized meaning of "specific" hybridization is that the nucleic acid molecule that specifically hybridizes to a particular nucleic acid sequence without binding to another nucleic acid sequence. Therefore, Claim 48 (and, as a consequence, those claims dependent from the same) clearly refers to a nucleic acid molecule or a complement thereof, that is able to bind to the nucleic acid sequence of SEQ ID NO:305 or a complement thereof, *without* binding to another nucleic acid molecule, including the sequence of Accession

No. AA584408.

Further, the Examiner admits that the nucleic acid sequence of Accession No. AA584408 is only 55.5% identical to SEQ ID NO:305 starting on nucleic acid residue 354 of SEQ ID NO:305 of the present application. See attached sequence alignment in instant Office Action. In view of this limited degree of sequence identity and the fact the claimed sequence will only specifically hybridize to the SEQ ID NO:305 or complement thereof, Claims 48-54 are not anticipated by the nucleic acid sequence of Accession No. AA584408. Accordingly, Applicants respectfully request to reconsider and withdraw the present rejection.

CONCLUSION

In conclusion, the present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Should there be any further issues outstanding, the Examiner is invited to contact the undersigned attorney at the telephone number shown below. Please charge any additional fees, including fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2830 P1C61**). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: November 12, 2004 By: _____

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